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L2: Entry 2 of 4

File: USPT

May 8, 2001

DOCUMENT-IDENTIFIER: US 6228347 B1

TITLE: Antioxidant gel for gingival conditions

Detailed Description Paragraph Right (16):

Other dental antiplaque oral compositions for gels and pastes have been patented with other compounds as optional ingredients. Gaffar in U.S. Pat. No. 5,472,685 issued Dec. 5, 1995, which is also incorporated herein by reference, teaches that the triclosan antimicrobial and antiplaque benefit is enhanced in the presence of a phenolic flavoring agent, such as menthol, eucalyptol or thymol. Antimicrobials may optionally be included in these gels and pastes to help decrease or eliminate the putative bacteria which contribute to the inflammatory reactions in gingivitis and periodontitis.

Detailed Description Paragraph Right (22):

Another method of application of the gel, paste, gum or lozenge of the present invention is to incorporate the various antioxidants, minerals and amino acids in liposomes or other state of the art encapsulating vehicles, akin to nanospheres, glycospheres and others as used in topical compositions. Liposomes are lecithin spheres that form an oil protective membrane around the putative active ingredients of the composition. These carriers also deliver the active ingredients locally for their preventive and therapeutic functions as well as systemically through buccal mucosal absorption. Unger and co-workers, in U.S. Pat. No. 5,580,575, issued Dec. 3, 1996, which is herein incorporated by reference, have taught therapeutic drug delivery systems comprising gas-filled liposomes which encapsulate the active preparation. Earlier, Chakrabarti and associates, in U.S. Pat. No. 5,380,531, issued Jan. 10, 1995, which is also herein incorporated by reference, disclosed preparations comprising a lipid and a modified peptide for incorporation into liposomes. In addition, Knight et al. (U.S. patent '388) has taught small particle aerosol liposomes and liposome combinations for medical delivery uses.

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L2: Entry 3 of 4

File: USPT

Sep 29, 1998

DOCUMENT-IDENTIFIER: US 5814343 A

TITLE: Cosmetic composition

Brief Summary Paragraph Right (6):

Similarly, W088/00824 contemplates targeting liposomes containing therapeutic agents to mucosal surfaces by means of positively charged groups at the surface of the liposomes.

Brief Summary Paragraph Right (29):

Benefit agents which may be employed in the compositions and methods of the invention include one or more of antimicrobials, anti-inflammatory agents, perfumes, antiperspirants, deodorants, sunscreens, antioxidants, hair growth agents, moisturising agents, cleansing agents and conditioning agents. It is preferred that the benefit agent be an antimicrobial. Examples include antibacterial agents having a molecular weight not greater than 2000. Within this category, biphenolic compounds are of interest, a preferred example being Triclosan (2,4,4'-trichloro-2'-hydroxy diphenyl ether) which is a broad spectrum antibacterial agent. Other antimicrobials include chlorhexidine, zinc pyrithione, farnesol, triethyl citrate, benzoic acid, benzyl benzoate, ethyl lactate, undecelenic acid, benzethonium chloride, and metal salts containing Zn.sup.2 +, Cu.sup.2 + or Ag+ and quaternary ammonium surfactants such as cetyl trimethyl ammonium bromide.

Detailed Description Paragraph Right (21):

The antibacterial efficacy of Triclosan delivered in targeted liposomes was assessed using a bacterial regrowth assay.

Detailed Description Paragraph Right (22):

Liposomes containing Triclosan were prepared as described above in Example 1(a) except that dipalmitoyl phosphatidyl glycerol (DPPG) was used in place of DPPC and Triclosan (6 .mu.g for 31 mg lipid) was added to the chloroform/methanol mixture employed in the first step of liposome formation. Phosphatidyl inositol was used as targeting molecule. Liposome fractions following gel filtration were analysed for phospholipid [.sup.14 C-DPPC] and Triclosan [.sup.3 H-tritiated] by scintillation counting. Particle size was determined and fractions having two different mean diameters were selected for use in the assay.

Detailed Description Paragraph Right (24):

200 .mu.l of test solution containing either liposomes with Triclosan, or an equivalent amount of free Triclosan all in PBS containing 10% ethanol (Triclosan is virtually insoluble in PBS alone; this level of ethanol does not kill the bacteria), was added to the well and allowed to adsorb for 2 minutes at 37.degree. C. The plate was then washed 3 times with sterile PBS, 200 .mu.l growth medium added (10% BHI plus 0.3% yeast extract) sealed and incubated for 18 h at 37.degree. C. After this incubation period, the plate was read using a Dynatech MR610 plate reader and the extent of continuing bacterial growth determined from the measured optical density at 630 nm.

Detailed Description Paragraph Right (25):

The results are set out in Table 6 and indicate that a higher percentage kill could be achieved with PI targeted liposomes than with an equivalent amount of free Triclosan.

Detailed Description Paragraph Table (6):

TABLE 6 STAPHYLOCOCCUS EPIDERMIDIS COMPOSITION
 (mg) d.sub.w Moles Lipid DPPG PI Triclosan (nm) per ml
 Initial VETs 27 4 0.006 92.0 1.41 .times.
 10.sup.-5 VETs 101.1 2.86 .times. 10.sup.-6 Fraction 11 VETs 94.1 9.68 .times.
 10.sup.-6 Fraction 12 REGROWTH ASSAY 2 Minute
 Exposure Time d.sub.w Moles Lipid .mu.g Triclosan (nm) per ml per ml % Kill
 VETs Fraction 101.1 2.86 .times. 10.sup.-6
 0.702 64.4 11 Free Triclosan -- -- 0.702 47.1 VETs Fraction 12 94.1 9.68 .times.
 10.sup.-6 0.225 54.9 Free Triclosan -- -- 0.225 40.4
 Free Triclosan and VET samples contained 10%
 Ethanol

Detailed Description Paragraph Table (7):

TABLE 7A STAPHYLOCOCCUS EPIDERMIDIS (with
Phosphatidyl Inositol as Targetting Species) COMPOSITION (mg) d.sub.w Moles Lipid
 DPPC PI Triclosan (nm) per ml Initial 27 4
 0.006 92.7 1.38 .times. 10.sup.-5 VETs VETs 91.5 5.10 .times. 10.sup.-6 Fraction 11
 VETs 88.6 4.60 .times. 10.sup.-6 Fraction 12
 REGROWTH ASSAY 2 minute exposure time Moles Lipid .mu.g Triclosan d.sub.w Per ml Per
 ml % Kill VETs 91.5 5.10 .times. 10.sup.-6
 0.497 20.7 Fraction 11 Free -- -- 0.497 14.3 Triclosan VETs 88.6 4.60 .times.
 10.sup.-6 0.283 21.9 Fraction 12 Free -- -- 0.283 15.8 Triclosan
 Free Triclosan and VET samples contained 10%
 Ethanol.

Detailed Description Paragraph Table (8):

TABLE 7B STAPHYLOCOCCUS EPIDERMIDIS (with
Phosphatidyl Inositol as Targetting Species) COMPOSITION (mg) d.sub.w Moles Lipid
 DPPC PI Triclosan (min) per ml Initial 27 4
 0.006 91.4 1.38 .times. 10.sup.-5 VETs VETs 87.7 4.83 .times. 10.sup.-6 Fraction 11
 VETs 83.9 4.96 .times. 10.sup.-6 Fraction 12
 REGROWTH ASSAY 2 minute exposure time Moles Lipid .mu.g Triclosan d.sub.w Per ml Per
 ml % Kill VETs 87.7 4.83 .times. 10.sup.-6
 0.451 18.4 Fraction 11 Free -- -- 0.451 8.9 Triclosan VETs 83.9 4.96 .times.
 10.sup.-6 0.433 18.4 Fraction 12 Free -- -- 0.433 8.8 Triclosan
 Free Triclosan and VET samples contained 10%
 Ethanol.

WEST[Generate Collection](#)[Print](#)**Search Results - Record(s) 1 through 4 of 4 returned.**☐ 1. Document ID: US 6306838 B1

L2: Entry 1 of 4

File: USPT

Oct 23, 2001

US-PAT-NO: 6306838

DOCUMENT-IDENTIFIER: US 6306838 B1

TITLE: Targeted vesicular constructs for cyto protection and treatment of h. pylori

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC
Draw Desc	Image										

☐ 2. Document ID: US 6228347 B1

L2: Entry 2 of 4

File: USPT

May 8, 2001

US-PAT-NO: 6228347

DOCUMENT-IDENTIFIER: US 6228347 B1

TITLE: Antioxidant gel for gingival conditions

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC
Draw Desc	Image										

☐ 3. Document ID: US 5814343 A

L2: Entry 3 of 4

File: USPT

Sep 29, 1998

US-PAT-NO: 5814343

DOCUMENT-IDENTIFIER: US 5814343 A

TITLE: Cosmetic composition

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC
Draw Desc	Image										

☐ 4. Document ID: US 5510120 A

L2: Entry 4 of 4

File: USPT

Apr 23, 1996

US-PAT-NO: 5510120

DOCUMENT-IDENTIFIER: US 5510120 A

TITLE: Cosmetic composition for topical application to skin or hair

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC
Draw. Desc	Image										

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L4: Entry 25 of 34

File: USPT

Dec 29, 1998

DOCUMENT-IDENTIFIER: US 5853753 A

TITLE: Liposomes, method of preparing the same and use thereof in the preparation of drugs

Brief Summary Paragraph Right (85):

Physiological liposomes are excellently suited for controlling skin or mucous membrane allergies. The term mucous membrane allergy predominantly covers allergic reactions of the nasal, buccal or ophthalmic mucous membrane which are triggered by contact with corresponding allergens. The immunological mechanisms which take place here are similar to those of the skin allergies discussed hereinafter with reference to the earring allergy. The term skin allergy covers syndromes of different geneses of which all, however, lead to a similar, more or less locally defined skin reaction (allergy).

Brief Summary Paragraph Right (101):

As already described in sections I and II, the physiological liposomes of the invention have antiviral and antiallergic properties that suggest their use as an ophthalmic agent. In addition to these therapeutical approaches, there are above all regeneration-supporting (see section I, point 8) and protective abilities of physiological liposomes. The front part of the eye, above all the cornea and the neighboring conjunctivae are coated by a permanent liquid film. Apart from nutrients, salts and antimicrobial substances, this lacrimal fluid also contains substances which prevent rapid evaporation (e.g. lipids and mucins). The composition of the lacrimal fluid wetting the cornea and conjunctivae follows from the secretion of various glands, with the lacrimal gland secreting the main part of the fluid. Alveolar sebaceous glands (Meibomian gland), apocrine glands (Moll's glands), as well as small accessory tear glands (Krause's glands) are seated in the eyelid itself. The bradytropic cornea, specifically the front cornea epithelium (5-6 layers of non-cornified epitheliums), is nourished by the lacrimal fluid through diffusion. This explains the special sensitivity of the cornea to disorders of the lacrimal fluid. As proved in Example 4 with reference to a group of patients having dry-eye symptoms, physiological liposomes, when applied externally to the eyelid, can contribute to a normalization of the fluid layer wetting the cornea and conjunctivae in many cases. The liposomes presumably penetrate through the very thin, multilayered cornified pavement epithelium of the front side of the eyelid, thereby supplying the lid-bound glands with fluid, nutrients and secretable substances (lipids) which slow down the evaporation of the eye fluid. Furthermore, studies with test persons having conjunctivitis caused by allergen or virus and with ceratitis show that upon application of physiological liposomes on the eyelid the "sand grain sensation" will disappear within a few minutes and the symptoms will decline in most cases within a day upon repeated application.

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L4: Entry 15 of 34

File: USPT

May 9, 2000

US-PAT-NO: 6060082

DOCUMENT-IDENTIFIER: US 6060082 A

TITLE: Polymerized liposomes targeted to M cells and useful for oral or mucosal drug delivery

DATE-ISSUED: May 9, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Chen; Hongming	Lansdale	PA		
Langer; Robert S.	Newton	MA		

US-CL-CURRENT: 424/450; 436/829

CLAIMS:

We claim:

1. Polymerized liposomes comprising a phospholipid bilayer having covalently bonded phospholipids, an aqueous core and a lectin wherein the lectin is Ulex Europeans Agglutinin I.
2. The liposomes of claim 1 further comprising an antigen, a biologically active molecule or a detectable molecule.
3. The liposome of claim 1 wherein the targeting molecule is modified Ulex Europaeus Agglutinin.
4. The liposomes of claim 2 wherein the biologically active molecule is selected from the group consisting of cells, viruses, vectors, proteins, peptides, nucleic acids, polysaccharides, carbohydrates, lipids, glycoproteins, drugs or combinations thereof.
5. The liposomes of claim 2 wherein the biologically active molecule is an antigen.
6. The liposomes of claim 5 wherein the antigen is influenza hemeagglutinin.
7. The liposomes of claim 5 wherein the antigen is the ospA antigen from Lyme disease bacteria.
8. The liposomes of claim 5 wherein the antigen is a fragment of diphtheria toxin.
9. The liposomes of claim 1 having a degree of crosslinking between 30 and 100 percent.
10. The liposomes of claim 1 comprising phospholipids selected from the group consisting of double bond-containing olefinic and acetylenic phospholipids and phospholipids containing thiol groups.
11. The liposomes of claim 1 having a diameter of between fifteen nm and ten microns.
12. The polymerized liposome of claim 1 wherein said phospholipid is DODPC.

13. The polymerized liposome of claim 12 wherein the polymerized liposome comprises about 85 to 100% DODPC.
14. A method of delivering therapeutic molecules to an animal which comprises administering to said animal polymerized liposomes comprising a phospholipid bilayer having covalently bonded phospholipids; an aqueous core; a lectin wherein the lectin is Ulex Europeans Agglutinin(UEA) therapeutic molecule.
15. The method of claim 14 further comprising at least one targeting molecule selected from the group consisting of glycoproteins, antibodies, antibody fragments, or cell surface receptors and ligands.
16. The method of claim 14 wherein the therapeutic molecule is a detectable compound selected from the group consisting of radiopaque substances, air, magnetic materials, or substances detectable by magnetic resonance imaging.
17. The method of claim 14 wherein the molecules are biologically active substances selected from the group consisting of cells, viruses, vectors, proteins, peptides, nucleic acids, polysaccharides and carbohydrates, lipids, glycoproteins, or combinations thereof, and synthetic organic and inorganic drugs exerting a biological effect when administered to an animal.
18. The method of claim 14 wherein the biologically active substance is an antigen and the liposomes are administered to the animal in an amount effective to elicit a humoral or cell mediated immune response against the antigen.
19. The method of claim 14 further comprising providing an adjuvant in the hydrophobic layer of the liposome.
20. The method of claim 14 wherein the administration is by an oral route.
21. The method of claim 14 wherein the administration of sublingual, buccal, or rectal.
22. The method of claim 14 wherein the administration is through mucosa.
23. A method of orally delivering therapeutics to a mammal which comprises administering to said mammal a polymerized liposome comprising a polymerized phospholipid bilayer, therapeutic agent encapsulated in an aqueous core of said liposome and a lectin wherein the lectin is Ulex Europeans Agglutinin(UEA).

☐

L4: Entry 7 of 34

File: USPT

May 8, 2001

US-PAT-NO: 6228347

DOCUMENT-IDENTIFIER: US 6228347 B1

TITLE: Antioxidant gel for gingival conditions

DATE-ISSUED: May 8, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hersh; Theodore	Atlanta	GA		

US-CL-CURRENT: 424/49; 424/401, 424/440, 424/441, 424/450, 424/464, 424/48, 424/52,
424/702, 514/458, 514/474, 514/725, 514/900, 514/902, 514/904, 514/944

CLAIMS:

What is claimed is:

1. A gel or paste composition for oral application to human gums to reduce symptoms of gum disease, said composition comprising a gel or paste-based carrier and, as active ingredients, an effective amount of reduced glutathione and a source of selenium to reduce said symptoms of gum disease.
2. The gel or paste composition of claim 1 wherein said source of selenium comprises a member selected from the group consisting of elemental selenium, a selenoamino acid, a selenium yeast extract and a selenium chelate.
3. The gel or paste composition of claim 2 wherein said selenoamino acid comprises a member selected from the group consisting of selenomethionine and selenocystine.
4. The gel or paste composition of claim 1 further comprising vitamin C as ascorbic acid or as a derivative of ascorbic acid.
5. The gel or paste composition of claim 1 further comprising vitamin E as alpha tocopherol.
6. The gel or paste composition of claim 1 further comprising superoxide dismutase.
7. The gel or paste composition of claim 1 further comprising vitamin A.
8. A method of reducing symptoms of periodontal disease in humans, said method comprising applying to human gums a gel or paste including, as active ingredients, an effective amount of reduced glutathione and a source of selenium.
9. The method of claim 8 wherein said source of selenium comprises a member selected from the group consisting of elemental selenium, a selenoamino acid, a selenium yeast extract and a selenium chelate.
10. The method of claim 9 wherein said selenoamino acid comprises a member selected from the group consisting of selenomethionine and selenocysteine.
11. The method of claim 8 further comprising applying vitamin C in said gel or paste as ascorbic acid or as a derivative of ascorbic acid to human gums.

12. The method of claim 8 further comprising applying vitamin E in said gel or paste as alpha tocopherol the human gums.
13. The method of claim 8 further comprising applying superoxide dismutase to human gums in said gel or paste.
14. The method of claims 8 further comprising applying vitamin A in human gums in said gel or paste.
15. The gel or paste of claim 1, further comprising a flavorant.
16. The gel or paste of claim 15 wherein said flavorant is xylitol.
17. The gel or paste of claim 1 wherein said active ingredients are encapsulated in a liposome.
18. The gel or paste of claim 1 further comprising an abrasive.
19. The gel or paste of claim 18 wherein said abrasive is a member selected from the group consisting of hydrated silica, calcium carbonate, sodium bicarbonate, dicalcium phosphate, bentonite clay and kaolin clay.
20. The gel of claim 19 further comprising fluoride.
21. A gum composition for oral application to human gums to reduce symptoms of gum disease, said composition comprising a gum-based carrier and, as active ingredients, an effective amount of reduce glutathione and a source of selenium.
22. A lozenge composition for oral application to human gums to reduce symptoms of gum disease, said composition comprising a lozenge-based carrier and, as active ingredients, an effective amount of reduce glutathione and a source of selenium.
23. The gel or paste composition of claim 1 further comprising an amino acid, cysteine.
24. The method of claim 8 further comprising applying an amino acid cysteine in said gel or paste to human gums.

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L4: Entry 3 of 34

File: USPT

Sep 18, 2001

US-PAT-NO: 6290987

DOCUMENT-IDENTIFIER: US 6290987 B1

TITLE: Mixed liposome pharmaceutical formulation with amphiphiles and phospholipids

DATE-ISSUED: September 18, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Modi; Pankaj	Ancaster			CAX

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Generex Pharmaceuticals, Inc.	Ontario			CAX	03

APPL-NO: 9/ 391664 [PALM]

DATE FILED: September 7, 1999

PARENT-CASE:

The present application is a continuation-in-part of application Ser. No. 09/161,447, filed Sep. 27, 1998, now U.S. Pat. No. 6,193,997, issued Feb. 27, 2001.

INT-CL: [7] A61 K 9/127

US-CL-ISSUED: 424/450; 424/400, 424/434, 424/464, 424/45, 424/46, 424/184.1, 424/198.1, 424/130.1, 424/725, 514/2

US-CL-CURRENT: 424/450; 424/130.1, 424/184.1, 424/198.1, 424/400, 424/434, 424/45, 424/46, 424/464, 424/725, 514/2

FIELD-OF-SEARCH: 424/45, 424/46, 424/195.1, 424/450, 424/400, 424/434, 424/464, 424/184.1, 424/198.1, 424/130.1, 424/725, 514/2

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected

Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
<input type="checkbox"/>	<u>4614730</u>	September 1986	Hansen et al.	
<input type="checkbox"/>	<u>4708861</u>	November 1987	Popescu et al.	
<input type="checkbox"/>	<u>4772471</u>	September 1988	Vanlerberghe et al.	
<input type="checkbox"/>	<u>4830857</u>	May 1989	Handjani et al.	
<input type="checkbox"/>	<u>4839111</u>	June 1989	Huang	
<input type="checkbox"/>	<u>4900730</u>	February 1990	Miyauchi	
<input type="checkbox"/>	<u>4921757</u>	May 1990	Wheatley et al.	
<input type="checkbox"/>	<u>5147723</u>	September 1992	Wallach	
<input type="checkbox"/>	<u>5230884</u>	July 1993	Evans et al.	
<input type="checkbox"/>	<u>5234767</u>	August 1993	Wallach	
<input type="checkbox"/>	<u>5260065</u>	November 1993	Mathur et al.	
<input type="checkbox"/>	<u>5292499</u>	March 1994	Evans et al.	
<input type="checkbox"/>	<u>5306483</u>	April 1994	Mautone	
<input type="checkbox"/>	<u>5376646</u>	December 1994	Pittrof et al.	
<input type="checkbox"/>	<u>5514670</u>	May 1996	Friedman et al.	
<input type="checkbox"/>	<u>5591713</u>	January 1997	Igari et al.	
<input type="checkbox"/>	<u>5643600</u>	July 1997	Mathur	
<input type="checkbox"/>	<u>5653987</u>	August 1997	Modi et al.	
<input type="checkbox"/>	<u>5665700</u>	September 1997	Cho et al.	
<input type="checkbox"/>	<u>5690954</u>	November 1997	Illum	
<input type="checkbox"/>	<u>6017545</u>	January 2000	Modi	

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
0 200 383	December 1986	EPX	
0 272 097	June 1988	EPX	
0 475 160	March 1992	EPX	
96 36352	November 1996	WOX	
99 40932	August 1999	WOX	

OTHER PUBLICATIONS

Kohler, D. (1993). Systemic Therapy with Aerosols. In: Aerosols in Medicine (Moren et al eds), Elsevier Science Publishers, pp. 303-319.*
Patton et al. (1992). Advanced Drug Delivery Reviews, vol. 8, pp. 179-196.

ART-UNIT: 169

PRIMARY-EXAMINER: Bawa; Raj

ATTY-AGENT-FIRM: Anderson; Debra Z. Eckert Seamans Cherin & Mellott, LLC

ABSTRACT:

A mixed liposome pharmaceutical formulation with multilamellar vesicles is provided. The formulation comprises a pharmaceutical agent, water, an alkali metal alkyl

sulfate, at least one membrane mimetic amphiphile, and at least one phospholipid. When aerosol delivery is intended, the formulation also comprises a propellant and a phenol. A metered dose dispenser containing the formulation, as well as a method of administering the formulation, are also provided.

34 Claims, 0 Drawing figures

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L4: Entry 31 of 34

File: USPT

Jul 26, 1994

US-PAT-NO: 5332582

DOCUMENT-IDENTIFIER: US 5332582 A

TITLE: Stabilization of aminosteroids for topical ophthalmic and other applications

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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[KVMC](#)☐ 32. Document ID: US 5534496 A

L4: Entry 32 of 34

File: EPAB

Jul 9, 1996

PUB-NO: US005534496A

DOCUMENT-IDENTIFIER: US 5534496 A

TITLE: Methods and compositions to enhance epithelial drug transport

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

[KVMC](#)☐ 33. Document ID: WO 9843616 A1, AU 9867935 A

L4: Entry 33 of 34

File: DWPI

Oct 8, 1998

DERWENT-ACC-NO: 1998-557053

DERWENT-WEEK: 199847

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TITLE: Liposome(s) which adhere to mucosa - comprise lipid, glycosyl:ceramide and optionally bioactive agent, useful for delivering drugs to systemic system

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

[KVMC](#)☐ 34. Document ID: WO 9408599 A1, AU 9351712 A

L4: Entry 34 of 34

File: DWPI

Apr 28, 1994

DERWENT-ACC-NO: 1994-150929

DERWENT-WEEK: 199832

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TITLE: Hydrophobic ion pair formation for improved partition into solvents - used esp. for proteins, polypeptide(s), enzymes (for reactions or therapy), or bitter-tasting drugs, also improves thermal stability

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KMOC
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L4: Entry 1 of 34

File: USPT

Feb 5, 2002

US-PAT-NO: 6344484

DOCUMENT-IDENTIFIER: US 6344484 B1

TITLE: Tyrosine alkoxyguanidines as integrin inhibitors

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

[KMC](#)☐ 2. Document ID: US 6339068 B1

L4: Entry 2 of 34

File: USPT

Jan 15, 2002

US-PAT-NO: 6339068

DOCUMENT-IDENTIFIER: US 6339068 B1

TITLE: Vectors and methods for immunization or therapeutic protocols

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

[KMC](#)☐ 3. Document ID: US 6290987 B1

L4: Entry 3 of 34

File: USPT

Sep 18, 2001

US-PAT-NO: 6290987

DOCUMENT-IDENTIFIER: US 6290987 B1

TITLE: Mixed liposome pharmaceutical formulation with amphiphiles and phospholipids

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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[KMC](#)☐ 4. Document ID: US 6271200 B1

L4: Entry 4 of 34

File: USPT

Aug 7, 2001

US-PAT-NO: 6271200

DOCUMENT-IDENTIFIER: US 6271200 B1

TITLE: Proteinic drug delivery system using aerosolized membrane-mimetic amphiphiles

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw	Desc	Image							

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☐ 5. Document ID: US 6248720 B1

L4: Entry 5 of 34

File: USPT

Jun 19, 2001

US-PAT-NO: 6248720

DOCUMENT-IDENTIFIER: US 6248720 B1

TITLE: Method for gene therapy using nucleic acid loaded polymeric microparticles

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw	Desc	Image							

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☐ 6. Document ID: US 6245523 B1

L4: Entry 6 of 34

File: USPT

Jun 12, 2001

US-PAT-NO: 6245523

DOCUMENT-IDENTIFIER: US 6245523 B1

TITLE: Survivin, a protein that inhibits cellular apoptosis, and its modulation

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw	Desc	Image							

KMIC

☐ 7. Document ID: US 6228347 B1

L4: Entry 7 of 34

File: USPT

May 8, 2001

US-PAT-NO: 6228347

DOCUMENT-IDENTIFIER: US 6228347 B1

TITLE: Antioxidant gel for gingival conditions

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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☐ 8. Document ID: US 6221855 B1

L4: Entry 8 of 34

File: USPT

Apr 24, 2001

US-PAT-NO: 6221855

DOCUMENT-IDENTIFIER: US 6221855 B1

TITLE: Regulation of nucleic acid expression by heparan sulfate and biological equivalents thereof

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

KMMC

☐ 9. Document ID: US 6207679 B1

L4: Entry 9 of 34

File: USPT

Mar 27, 2001

US-PAT-NO: 6207679

DOCUMENT-IDENTIFIER: US 6207679 B1

TITLE: Antimicrobial agents uses and compositions related thereto

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

KMMC

☐ 10. Document ID: US 6193997 B1

L4: Entry 10 of 34

File: USPT

Feb 27, 2001

US-PAT-NO: 6193997

DOCUMENT-IDENTIFIER: US 6193997 B1

TITLE: Proteinic drug delivery system using membrane mimetics

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

KMMC

☐ 11. Document ID: US 6187335 B1

L4: Entry 11 of 34

File: USPT

Feb 13, 2001

US-PAT-NO: 6187335

DOCUMENT-IDENTIFIER: US 6187335 B1

TITLE: Polymerizable fatty acids, phospholipids and polymerized liposomes therefrom

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

KMMC

☐ 12. Document ID: US 6180640 B1

L4: Entry 12 of 34

File: USPT

Jan 30, 2001

US-PAT-NO: 6180640

DOCUMENT-IDENTIFIER: US 6180640 B1

TITLE: Di- and tetra-hydroquinoline-indole antimicrobial agents, uses and compositions related thereto

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

KMMC

☐ 13. Document ID: US 6172084 B1

L4: Entry 13 of 34

File: USPT

Jan 9, 2001

US-PAT-NO: 6172084

DOCUMENT-IDENTIFIER: US 6172084 B1

TITLE: Quinoline-indole antimicrobial agents, uses and compositions related thereto

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KVMC
Draw Desc	Image									

☐ 14. Document ID: US 6103905 A

L4: Entry 14 of 34

File: USPT

Aug 15, 2000

US-PAT-NO: 6103905

DOCUMENT-IDENTIFIER: US 6103905 A

TITLE: Quinoline-indole antimicrobial agents, uses and compositions related thereto

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KVMC
Draw Desc	Image									

☐ 15. Document ID: US 6060082 A

L4: Entry 15 of 34

File: USPT

May 9, 2000

US-PAT-NO: 6060082

DOCUMENT-IDENTIFIER: US 6060082 A

TITLE: Polymerized liposomes targeted to M cells and useful for oral or mucosal drug delivery

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KVMC
Draw Desc	Image									

☐ 16. Document ID: US 6045788 A

L4: Entry 16 of 34

File: USPT

Apr 4, 2000

US-PAT-NO: 6045788

DOCUMENT-IDENTIFIER: US 6045788 A

TITLE: Method of stimulation of immune response with low doses of IL-2

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KVMC
Draw Desc	Image									

☐ 17. Document ID: US 6004534 A

L4: Entry 17 of 34

File: USPT

Dec 21, 1999

US-PAT-NO: 6004534

DOCUMENT-IDENTIFIER: US 6004534 A

TITLE: Targeted polymerized liposomes for improved drug delivery

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

KVMC

☐ 18. Document ID: US 5985847 A

L4: Entry 18 of 34

File: USPT

Nov 16, 1999

US-PAT-NO: 5985847

DOCUMENT-IDENTIFIER: US 5985847 A

TITLE: Devices for administration of naked polynucleotides which encode biologically active peptides

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

KVMC

☐ 19. Document ID: US 5985608 A

L4: Entry 19 of 34

File: USPT

Nov 16, 1999

US-PAT-NO: 5985608

DOCUMENT-IDENTIFIER: US 5985608 A

TITLE: Actin-binding polypeptides and nucleic acids encoding the same

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

KVMC

☐ 20. Document ID: US 5985275 A

L4: Entry 20 of 34

File: USPT

Nov 16, 1999

US-PAT-NO: 5985275

DOCUMENT-IDENTIFIER: US 5985275 A

TITLE: .beta.-Lactoglobulin modified with aromatic anhydride compound for preventing HIV infection

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

KVMC

☐ 21. Document ID: US 5981474 A

L4: Entry 21 of 34

File: USPT

Nov 9, 1999

US-PAT-NO: 5981474

DOCUMENT-IDENTIFIER: US 5981474 A

TITLE: Solubilization of pharmaceutical substances in an organic solvent and preparation of pharmaceutical powders using the same

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

K00C

☐ 22. Document ID: US 5922346 A

L4: Entry 22 of 34

File: USPT

Jul 13, 1999

US-PAT-NO: 5922346

DOCUMENT-IDENTIFIER: US 5922346 A

TITLE: Antioxidant preparation

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

K00C

☐ 23. Document ID: US 5906811 A

L4: Entry 23 of 34

File: USPT

May 25, 1999

US-PAT-NO: 5906811

DOCUMENT-IDENTIFIER: US 5906811 A

TITLE: Intra-oral antioxidant preparations

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

K00C

☐ 24. Document ID: US 5871723 A

L4: Entry 24 of 34

File: USPT

Feb 16, 1999

US-PAT-NO: 5871723

DOCUMENT-IDENTIFIER: US 5871723 A

TITLE: CXC chemokines as regulators of angiogenesis

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

K00C

☐ 25. Document ID: US 5853753 A

L4: Entry 25 of 34

File: USPT

Dec 29, 1998

US-PAT-NO: 5853753

DOCUMENT-IDENTIFIER: US 5853753 A

TITLE: Liposomes, method of preparing the same and use thereof in the preparation of drugs

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

KVMC

☐ 26. Document ID: US 5830877 A

L4: Entry 26 of 34

File: USPT

Nov 3, 1998

US-PAT-NO: 5830877

DOCUMENT-IDENTIFIER: US 5830877 A

TITLE: Method, compositions and devices for administration of naked polynucleotides which encode antigens and immunostimulatory

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

KVMC

☐ 27. Document ID: US 5770559 A

L4: Entry 27 of 34

File: USPT

Jun 23, 1998

US-PAT-NO: 5770559

DOCUMENT-IDENTIFIER: US 5770559 A

TITLE: Solubilization of pharmaceutical substances in an organic solvent and preparation of pharmaceutical powders using the same

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

KVMC

☐ 28. Document ID: US 5656284 A

L4: Entry 28 of 34

File: USPT

Aug 12, 1997

US-PAT-NO: 5656284

DOCUMENT-IDENTIFIER: US 5656284 A

TITLE: Oral transmucosal delivery tablet and method of making it

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

KVMC

☐ 29. Document ID: US 5538721 A

L4: Entry 29 of 34

File: USPT

Jul 23, 1996

US-PAT-NO: 5538721

DOCUMENT-IDENTIFIER: US 5538721 A

TITLE: Stabilization of aminosteroids for topical ophthalmic and other applications

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KWIC
Draw Desc	Image									

☐ 30. Document ID: US 5534496 A

L4: Entry 30 of 34

File: USPT

Jul 9, 1996

US-PAT-NO: 5534496

DOCUMENT-IDENTIFIER: US 5534496 A

TITLE: Methods and compositions to enhance epithelial drug transport

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KWIC
Draw Desc	Image									

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WEST**End of Result Set**☐ **Generate Collection** **Print**

L7: Entry 1 of 1

File: USPT

Sep 26, 2000

DOCUMENT-IDENTIFIER: US 6123923 A

TITLE: Optoacoustic contrast agents and methods for their use

Detailed Description Paragraph Right (98):

Compounds used to make mixed micelle systems may be used as basic or auxiliary stabilizing materials, and include, for example, sodium dodecyl sulfate, cetylammmonium halides, cetylalkylammmonium halides, lauryltrimethylammmonium bromide (dodecyl-), cetyltrimethylammmonium bromide (hexadecyl-), myristyltrimethylammmonium bromide (tetradecyl-), alkylldimethylbenzylammmonium chloride (where alkyl is C.sub.12, C.sub.14 or C.sub.16,), benzylldimethyldodecylammmonium bromide/chloride, benzylldimethyl hexadecyl-ammmonium bromide/chloride, benzylldimethyl tetradecylammmonium halide (e.g, bromide/chloride, cetylldimethylethylammmonium halide bromide/chloride, or cetylpyridinium bromide/chloride.

Detailed Description Paragraph Right (374):

The compositions of the invention may be administered to a patient by a variety of different means. The means of administration will vary depending upon the intended application. As one skilled in the art would recognize, administration of the compositions, stabilizing materials and/or vesicles of the present invention can be carried out in various fashions, for example, topically, including ophthalmic, dermal, ocular and rectal, intrarectally, transdermally, orally, intraperitoneally, parenterally, intravenously, intravascularly, intralymphatically, intratumorly, intramuscularly, interstitially, intraarterially, subcutaneously, intraocularly, intrasynovially, transepithelially, pulmonarily via inhalation, ophthalmically, sublingually, buccally, or via nasal inhalation via insufflation or nebulization.

Detailed Description Paragraph Right (377):

The compositions, stabilizing materials and/or vesicles of the present invention are especially useful for targeting ligands that may be degraded in aqueous media or upon exposure to oxygen and/or atmospheric air. For example, vesicles may be filled with an inert gas for use with labile targeting ligands. Additionally, the compositions may be filled with an inert gas and used to encapsulate a labile targeting ligand for use in a region of a patient that would normally cause the targeting ligand to be exposed to atmospheric air, such as cutaneous and ophthalmic applications.

Detailed Description Paragraph Right (378):

For topical applications, the stabilizing materials and/or vesicles may be used alone, may be mixed with one or more solubilizing agents, such as dimethylsulfoxide (DMSO), or may be used with a delivery vehicle, and applied to the skin or mucosal membranes. Penetrating and/or solubilizing agents useful for the topical application of the stabilizing materials and/or vesicles are well known in the art. Stabilizing materials and/or vesicles formulated with penetration enhancing agents may be administered transdermally in a patch or reservoir with a permeable membrane applied to the skin. The use of rupturing ultrasound may increase transdermal delivery of photoactive agents. Further, a mechanism may be used to monitor and modulate delivery of the photoactive agents. For example, ultrasound may be used to visually monitor the bursting of the gas filled vesicles and modulate delivery of the photoactive agents and/or bioactive agents and/or a hydrophone may be used to detect the sound of the bursting of the gas filled vesicles and modulate delivery of the photoactive agents and/or bioactive agents.

Detailed Description Paragraph Right (428):

1.5 g of a fluorescein-derivatized diacylphosphatidyl ethanolamine and 3 g of soybean oil were agitated in a vortex mixer. Diacylphosphatidyl ethanolamine was derivatized with fluorescein by methods known in the art including those described by Ahlers et al, Biophys. J, 63:823-838 (1992), the disclosure of which is hereby incorporated by reference herein in its entirety. To this mixture was added 1.0 g of a lipid blend comprising 82 mol % dipalmitoylphosphatidylcholine, 10 mol % dipalmitoylphosphatidic acid and 8 mol % dipalmitoylphosphatidylethanol-amine-PEG5000 (all phospholipids from Avanti Polar Lipids, Alabaster, Ala.). The mixture was stirred for 10 minutes at 50.degree. C. then transferred into a container with 200 mls normal saline plus 1% w/v Pluronic F-65 and emulsified with a Microfluidizer (10.times.) at 16,000 psi while the temperature was maintained at 50.degree. C. The material was then subdivided into 1.0 ml aliquots in 1.5 ml vials. The vials were vacuum-evacuated, and the headspace was filled with perfluorobutane. The vials were sealed and shaken on an ESPE Capmix for 60 seconds at 4,500 rpm (alternatively, the vials may be placed on a Wig-L-Bug (Crescent Dental, Lyons Ill.) and agitated at 2800 rpm for 2 minutes). The resulting product was a suspension of a fluorescent lipid in oil filled liposomes or lipospheres (i.e., vesicles) containing about 0.45% by weight fluorophore and 0.45% by weight other lipids. The final product comprised acoustically and optically active lipospheres instilled with perfluorobutane gas, with a mean diameter under 10 .mu.m.

Detailed Description Paragraph Right (436):

As shown in Figures, the form of the delivery vehicle can be a solid matrix drug (as illustrated in FIG. 5) or acoustically active liposphere (as illustrated in FIG. 4) or a lipid vesicle (as illustrated in FIG. 7). The delivery vehicles entrap an echogenic gas or gaseous precursor and present targeting ligands for delivery to receptors at the site requiring therapy. The vehicles incorporate a photoactive agent which may be a drug (e.g., a bioactive agent) or accompany a drug.

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L8: Entry 7 of 37

File: USPT

Oct 26, 1999

DOCUMENT-IDENTIFIER: US 5972892 A

TITLE: Topical composition containing a substance P antagonist

Detailed Description Paragraph Table (1):

Example 1: Acne treatment cream for the face (oil-in- water emulsion) Sendide 0.15% Glycerol stearate 2% Polysorbate 60 (Tween 60 sold by 1% the company ICI) Stearic acid 1.4% n-Octanoyl-5-salicylic acid 1% Triethanolamine 0.7% Carbomer 0.4% Liquid fraction of shea butter 12% Perhydrosqualene 12% Antioxidant 0.05% Perfume 0.5% Preservative 0.3% Water qs 100%

Example 2: Emulsified care gel against insect bites (oil-in-water emulsion) Cyclomethicone 3% Purcellin oil (sold by the company Dragocco) 7% PEG-6/PEG-32/glycol stearate 0.3% (Tefose .RTM. 63 from Gattefosse) Spantide II 0.02% Preservative 0.3% Perfume 0.4% Carbomer 0.6% Crotamiton 5% Glycyrrhetic acid 2% Ethyl alcohol 5% Triethanolamine 0.2% Water qs 100%

Example 3: Acne rosacea care cream for the face (oil- in-water emulsion) Spantide II 0.25% Glycerol stearate 2% Polysorbate 60 (Tween 60 sold by 1% the company ICI) Stearic acid 1.4% Metronidazole 1% Triethanolamine 0.7% Carbomer 0.4% Liquid fraction of shea butter 12% Liquid paraffin 12% Antioxidant 0.05% Perfume 0.5% Preservative 0.3% Water qs 100%

Example 4: gel for the treatment of acne All-trans-retinoic acid 0.05% N,N'-bis-di(3,5-dimethylbenzyl)- 5% ethylenediamine Hydroxypropyl cellulose (Klucel H sold by 1% the company Hercules) Antioxidant 0.05% Isopropanol 40% Preservative 0.3% Water qs 100%

Example 5: Peeling lotion for the face Glycolic acid 50% Sodium hydroxide qs pH 2.8 Hydroxyethyl cellulose 0.5% N,N'-bis-di(3,5-dimethoxybenzyl)- 5% ethylenediamine Ethanol qs 100%

This lotion is used to remove the cicatrices left for example by acne.

Example 6: W/O emulsion for the treatment of dry skins, or of xeroses Abli EM 90 from Goldschmidt 2.5% (cetyldimethicone copolyol) DC 344 fluid from Dow Corning 15% (cyclomethicone) DC 593 fluid from Dow Corning 3.5% (cyclomethicone) Witconol APM from Witco (polypropylene 6% glycol-myristyl ether containing 3 mol of propylene glycol) Sendide 0.2% Glycerine 3% Lactic acid 5% NH.sub.3 (32% solution) qs pH = 4 NaCl 0.6% Preservative 0.15% Water qs 100%

Example 7: Cream for the treatment of acne (dispersion of liposomes) Chimexane NS/dimyristyl phosphate 5% (weight ratio 95/5) Salicylic acid 0.5% N,N'-bis-di(3,5-dimethoxybenzyl)- 4% ethylenediamine Glycerine 4% Vegetable oil 3% Volatile silicone oil 4.5% Triclosan 0.2% Carboxyvinyl polymer 0.9% Sodium hydroxide 1.8% Preservatives 0.8% Water qs 100%

Example 8: Cream for the treatment of acne (dispersion of liposomes) Chimexane NS 5% Glycolic acid 0.8% N,N'-bis-di(3,5-dimethylbenzyl)- 4% ethylenediamine Glyceryl 4% Hydrogenated isoparaffin 3% Carboxyvinyl polymer 0.9% Sodium hydroxide 1.8% Preservatives 0.6% Antioxidants 0.2% Water qs 100%

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L8: Entry 9 of 37

File: USPT

Mar 30, 1999

DOCUMENT-IDENTIFIER: US 5888995 A

TITLE: Steroid esters

Brief Summary Paragraph Right (41):

In addition to the main liposome-forming lipid(s) which is usually phospholipid, other lipids (e.g. cholesterol or cholesterol stearate) in the amount of 0-40% w/w of the total lipids may be included to modify the structure of the liposome membrane. In optimizing the uptake of the liposome a third component providing a negative charge (e.g. dipalmitoyl phosphatidyl glycerol) or a positive charge (e.g. stearylamine acetate or cetylpyridinium chloride) may be incorporated.

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L8: Entry 28 of 37

File: USPT

Jul 7, 1992

DOCUMENT-IDENTIFIER: US 5128139 A

TITLE: Composition containing liposome-entrapped grapefruit seed extract and method for making

Abstract Paragraph Left (1):

A composition is disclosed which comprises a phospholipid mixture and one or more bioactive agents formed into multilamellar liposomes wherein the bioactive agents are bound. Bioactive agents which are particularly suitable to the invention include grapefruit seed extract and Triclosan. A composition for a topical preparation including the multilamellar composition is also disclosed. Methods for preparing the compositions are further disclosed.

Detailed Description Paragraph Right (1):

The present invention generally comprises a liposome component, a bioactive substance or substances entrapped in the liposome component, and a base for applying the bioactive substance-bound liposome to the area of application. The bioactive substance or substances include extracts from the seeds of citrus fruits, which extracts display bacteriostatic properties. Citrus seed extracts, such as grapefruit seed extract, are commercially available. Citrus seed extracts generally include vitamin C and proteins. Another bioactive substance which may be used is Triclosan (2,4,4'-Trichloro-2'-hydroxydiphenyl ether) which is an antibacterial agent available from Ciba-Geigy (Greensboro, N.C.) and other suppliers. Triclosan is well known in the art.

Detailed Description Paragraph Right (2):

In the process of liposome formation, most of the Triclosan and grapefruit seed extract is entrapped within the liposomes. Some Triclosan and grapefruit seed extract may not be entrapped within the liposomes, and it is not necessary to remove or filter out the non-bound material. The presence of non-encapsulated Triclosan and grapefruit seed extract may, when used in a skin-care composition, provide advantageous initial bacteriostatic properties. The liposomes formed by this process may form into multiple layers. The procedure also forms liposomes of various size and shape.

Detailed Description Paragraph Right (8):

The mixture was then co-solubilized with 0.8 grams of grapefruit seed extract P-50 which is available from Chemie Research (Casselberry, Fla.). To the mixture was added 0.5 grams of Triclosan and the mixture was stirred. Finally, four milliliters of distilled water was added to the mixture and mixed rapidly. The addition of distilled water caused the lipid fraction of the mixture to form liposome vesicles.

Detailed Description Paragraph Right (10):

A liposome composition was prepared by co-solubilizing 0.8 grams of grapefruit seed extract with 0.25 grams of pre-liposome phospholipid mixture. To that mixture was added 0.5 grams of Triclosan and the mixture was stirred. Four (4) milliliters of distilled water were then added to the mixture to form the liposomes.

Detailed Description Paragraph Right (11):

A liposome composition was prepared by adding one (1) milliliter of ethanol to 0.25 grams of pre-liposome phospholipid mixture with stirring. Then 0.5 grams of Triclosan were added and the mixture was stirred. Thereafter, four milliliters of distilled water were added to the other ingredients to form the liposomes.

Detailed Description Paragraph Right (13):

A liposome composition was prepared by adding 1 ml of ethanol to 0.25 grams of pre-liposome phospholipid mixture. The resulting mixture was co-solubilized with 0.8 grams of grapefruit seed extract. Then 0.09 ml of grapefruit oil, as a fragrance, was added simultaneously with 0.5 grams of Triclosan to the previous mixture and the mixture was stirred. Finally, 4 ml of distilled water were added to the mixture to form the liposome.

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L8: Entry 29 of 37

File: USPT

Jun 19, 1990

DOCUMENT-IDENTIFIER: US 4935244 A

TITLE: Nedocromil sodium compositions and methods for their preparation

Brief Summary Paragraph Right (11):

A wide variety of lipid materials may be used to form the liposomes including natural lecithins, e.g. those derived from egg and soya bean, and synthetic lecithins. Lipids which are non-immunogenic and bio-degradable are preferred. The properties of the lipid, for example its phase transition temperature, can have a marked effect on the retention and uptake of the liposomes in the target organ and for this reason the well defined synthetic lecithins are preferred to the natural lecithins. Examples of synthetic lecithins which may be used, together with their respective phase transition temperatures, are di-(tetradecanoyl)phosphatidylcholine (DTPC) (23.degree. C.), di-(hexadecanoyl)phosphatidylcholine (DHPC) (41.degree. C.) and di-(octadecanoyl)phosphatidylcholine (DOPC) (55.degree. C.). We prefer to use di-(hexadecanoyl)phosphatidylcholine as the sole or major lecithin, optionally together with a minor proportion of the di-(octadecanoyl) or the di-(tetradecanoyl) compound. Other synthetic lecithins which may be used are unsaturated synthetic lecithins, for example di-(oleyl)phosphatidylcholine and di-(linoleyl)phosphatidylcholine. We prefer the synthetic lecithin, or the mixture of lipids, to have a phase transition temperature in the range 35.degree.-45.degree. C. In addition to the main liposome-forming lipid or lipids, which are usually phospholipids, other lipids (e.g. in a proportion of 5-40% w/w of the total lipids) may be included, for example cholesterol or cholesterol stearate, to modify the structure of the liposome membrane, rendering it more fluid or more rigid depending on the nature of the main liposome-forming lipid or lipids. An optional third component is a material which provides a negative charge, for example phosphatidic acid, dicetyl phosphate or beef brain ganglioside, or one which provides a positive charge for example stearylamine acetate or cetylpyridinium chloride. The charged component may be included in a proportion of 1-20% w/w of the total lipids.

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L8: Entry 34 of 37

File: EPAB

Sep 7, 1994

DOCUMENT-IDENTIFIER: EP 613685 A1

TITLE: Chlorhexidine diacetate or chlorhexidine digluconate containing liposomes.Abstract (1):

CHG DATE=19990617 STATUS=O> Liposomes which contain encapsulated chlorhexidine diacetate or chlorhexidine digluconate and whose composition comprises, besides bilayer-forming lipids, additionally surfactants are described. Advantages which may be mentioned for liposomal administration compared with the free form of chlorhexidine are higher and longer activity and fewer side effects.

WEST**End of Result Set**

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L8: Entry 37 of 37

File: DWPI

May 30, 1988

DERWENT-ACC-NO: 1988-188027

DERWENT-WEEK: 198827

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TITLE: Antimicrobial dermatological liposome prepn. - comprises lipid(s) contg. sparingly water-soluble antimicrobials or fungicide< br>

Basic Abstract Text:

The sparingly water soluble component is absorbed onto the surface of lamella of complex lipids. A conventional method is used for the prepn. of liposome. Complex lipids include natural phospholipids such as lecithin, sphingomyelin, synthetic phospholipids such as dipalmitoyl lecithin, dicetyl phosphate, natural or synthetic glycolipids such as glycosyl ceramide, glycosyldipalmitoylglycerol. Sterols such as cholesterol or stigmasterol can be added to stabilise the compsn. Antimicrobials include p-chloro m-cresol, p-hydroxybenzoic acid esters, chlorhexidine, etc.

Basic Abstract Text (2):

The sparingly water soluble component is absorbed onto the surface of lamella of complex lipids. A conventional method is used for the prepn. of liposome. Complex lipids include natural phospholipids such as lecithin, sphingomyelin, synthetic phospholipids such as dipalmitoyl lecithin, dicetyl phosphate, natural or synthetic glycolipids such as glycosyl ceramide, glycosyldipalmitoylglycerol. Sterols such as cholesterol or stigmasterol can be added to stabilise the compsn. Antimicrobials include p-chloro m-cresol, p-hydroxybenzoic acid esters, chlorhexidine, etc.

WEST[Generate Collection](#)[Print](#)**Search Results - Record(s) 31 through 37 of 37 returned.**☐ 31. Document ID: US 4804678 A

L8: Entry 31 of 37

File: USPT

Feb 14, 1989

US-PAT-NO: 4804678

DOCUMENT-IDENTIFIER: US 4804678 A

TITLE: Method for treating allergic conditions

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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[KVMC](#)☐ 32. Document ID: US 4693999 A

L8: Entry 32 of 37

File: USPT

Sep 15, 1987

US-PAT-NO: 4693999

DOCUMENT-IDENTIFIER: US 4693999 A

TITLE: Liposomes containing steroid esters

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

[KVMC](#)☐ 33. Document ID: US 4687661 A

L8: Entry 33 of 37

File: USPT

Aug 18, 1987

US-PAT-NO: 4687661

DOCUMENT-IDENTIFIER: US 4687661 A

TITLE: Method for producing liposomes

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

[KVMC](#)☐ 34. Document ID: EP 613685 A1

L8: Entry 34 of 37

File: EPAB

Sep 7, 1994

PUB-NO: EP000613685A1

DOCUMENT-IDENTIFIER: EP 613685 A1

TITLE: Chlorhexidine diacetate or chlorhexidine digluconate containing liposomes.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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KVMC

☐ 35. Document ID: US 5128139 A

L8: Entry 35 of 37

File: EPAB

Jul 7, 1992

PUB-NO: US005128139A

DOCUMENT-IDENTIFIER: US 5128139 A

TITLE: Composition containing liposome-entrapped grapefruit seed extract and method for making

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

KVMC

☐ 36. Document ID: ES 2124328 T3, EP 613685 A1, DE 4306475 A1, EP 613685 B1, DE 59407247 G

L8: Entry 36 of 37

File: DWPI

Feb 1, 1999

DERWENT-ACC-NO: 1994-272802

DERWENT-WEEK: 199911

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TITLE: Liposomes contg. encapsulated chlorhexidine di:acetate or di:gluconate - for use in dentistry and oral hygiene, without causing discoloration of the teeth, and for general wound disinfection.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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KVMC

☐ 37. Document ID: JP 63126820 A, JP 95061940 B2

L8: Entry 37 of 37

File: DWPI

May 30, 1988

DERWENT-ACC-NO: 1988-188027

DERWENT-WEEK: 198827

COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Antimicrobial dermatological liposome prepn. - comprises lipid(s) contg. sparingly water-soluble antimicrobials or fungicide

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

KVMC

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liposome\$ same (cetrimide or chlorhexidine or cetylpyridinium or triclosan)	37

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WEST[Generate Collection](#)[Print](#)**Search Results - Record(s) 1 through 16 of 16 returned.**☐ 1. Document ID: US 6071495 A

L9: Entry 1 of 16

File: USPT

Jun 6, 2000

US-PAT-NO: 6071495

DOCUMENT-IDENTIFIER: US 6071495 A

TITLE: Targeted gas and gaseous precursor-filled liposomes

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KMOC
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☐ 2. Document ID: US 5935553 A

L9: Entry 2 of 16

File: USPT

Aug 10, 1999

US-PAT-NO: 5935553

DOCUMENT-IDENTIFIER: US 5935553 A

TITLE: Methods of preparing gas-filled liposomes

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KMOC
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☐ 3. Document ID: US 5853752 A

L9: Entry 3 of 16

File: USPT

Dec 29, 1998

US-PAT-NO: 5853752

DOCUMENT-IDENTIFIER: US 5853752 A

TITLE: Methods of preparing gas and gaseous precursor-filled microspheres

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KMOC
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☐ 4. Document ID: US 5814343 A

L9: Entry 4 of 16

File: USPT

Sep 29, 1998

US-PAT-NO: 5814343

DOCUMENT-IDENTIFIER: US 5814343 A

TITLE: Cosmetic composition

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KVMC
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☐ 5. Document ID: US 5770222 A

L9: Entry 5 of 16

File: USPT

Jun 23, 1998

US-PAT-NO: 5770222

DOCUMENT-IDENTIFIER: US 5770222 A

TITLE: Therapeutic drug delivery systems

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KVMC
Draw Desc	Image									

☐ 6. Document ID: US 5769080 A

L9: Entry 6 of 16

File: USPT

Jun 23, 1998

US-PAT-NO: 5769080

DOCUMENT-IDENTIFIER: US 5769080 A

TITLE: Gas filled liposomes and stabilized gas bubbles and their use as ultrasonic contrast agents

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KVMC
Draw Desc	Image									

☐ 7. Document ID: US 5715824 A

L9: Entry 7 of 16

File: USPT

Feb 10, 1998

US-PAT-NO: 5715824

DOCUMENT-IDENTIFIER: US 5715824 A

TITLE: Methods of preparing gas-filled liposomes

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KVMC
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☐ 8. Document ID: US 5585112 A

L9: Entry 8 of 16

File: USPT

Dec 17, 1996

US-PAT-NO: 5585112

DOCUMENT-IDENTIFIER: US 5585112 A

TITLE: Method of preparing gas and gaseous precursor-filled microspheres

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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K00C

☐ 9. Document ID: US 5580575 A

L9: Entry 9 of 16

File: USPT

Dec 3, 1996

US-PAT-NO: 5580575

DOCUMENT-IDENTIFIER: US 5580575 A

TITLE: Therapeutic drug delivery systems

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

K00C

☐ 10. Document ID: US 5542935 A

L9: Entry 10 of 16

File: USPT

Aug 6, 1996

US-PAT-NO: 5542935

DOCUMENT-IDENTIFIER: US 5542935 A

TITLE: Therapeutic delivery systems related applications

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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K00C

☐ 11. Document ID: US 5510120 A

L9: Entry 11 of 16

File: USPT

Apr 23, 1996

US-PAT-NO: 5510120

DOCUMENT-IDENTIFIER: US 5510120 A

TITLE: Cosmetic composition for topical application to skin or hair

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

K00C

☐ 12. Document ID: US 5469854 A

L9: Entry 12 of 16

File: USPT

Nov 28, 1995

US-PAT-NO: 5469854

DOCUMENT-IDENTIFIER: US 5469854 A

TITLE: Methods of preparing gas-filled liposomes

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
Draw Desc	Image								

K00C

☐ 13. Document ID: US 5348016 A

L9: Entry 13 of 16

File: USPT

Sep 20, 1994

US-PAT-NO: 5348016

DOCUMENT-IDENTIFIER: US 5348016 A

TITLE: Apparatus for preparing gas filled liposomes for use as ultrasonic contrast agents

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	K/M/C
Draw Desc	Image									

☐ 14. Document ID: US 5305757 A

L9: Entry 14 of 16

File: USPT

Apr 26, 1994

US-PAT-NO: 5305757

DOCUMENT-IDENTIFIER: US 5305757 A

TITLE: Gas filled liposomes and their use as ultrasonic contrast agents

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	K/M/C
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☐ 15. Document ID: US 5228446 A

L9: Entry 15 of 16

File: USPT

Jul 20, 1993

US-PAT-NO: 5228446

DOCUMENT-IDENTIFIER: US 5228446 A

TITLE: Gas filled liposomes and their use as ultrasonic contrast agents

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	K/M/C
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☐ 16. Document ID: ES 2124328 T3, EP 613685 A1, DE 4306475 A1, EP 613685 B1, DE 59407247 G

L9: Entry 16 of 16

File: DWPI

Feb 1, 1999

DERWENT-ACC-NO: 1994-272802

DERWENT-WEEK: 199911

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TITLE: Liposomes contg. encapsulated chlorhexidine di:acetate or di:gluconate - for use in dentistry and oral hygiene, without causing discoloration of the teeth, and for general wound disinfection.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	K/M/C
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l8 and (mucosal or ophthalmic or buccal)	16

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☐ 1. Document ID: ES 2124822 T3, EP 639373 A1, JP 07145081 A, EP 639373 B1, DE 69414936 E, US 5863556 A

L5: Entry 1 of 3

File: DWPI

Feb 16, 1999

DERWENT-ACC-NO: 1995-083259

DERWENT-WEEK: 199914

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TITLE: Pharmaceutical compsn. comprises liposome prepn. of antiseptic and/or wound-healing agent - used to treat e.g. bacterial and viral kerato-conjun ctivitis and for pre-operative antiseptic prophylaxis

INVENTOR: FLEISCHER, W; GUEMBEL, H ; REIMER, K ; RUECKERT, D ; WINKLER, H

PRIORITY-DATA: 1993DE-0012509 (August 20, 1993)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
ES 2124822 T3	February 16, 1999		000	A61K009/127
EP 639373 A1	February 22, 1995	E	010	A61K009/127
JP 07145081 A	June 6, 1995		007	A61K045/00
EP 639373 B1	December 2, 1998	E	000	A61K009/127
DE 69414936 E	January 14, 1999		000	A61K009/127
US 5863556 A	January 26, 1999		000	A61K031/79

INT-CL (IPC): A01 N 25/26; A61 K 9/06; A61 K 9/127; A61 K 31/015; A61 K 31/05; A61 K 31/055; A61 K 31/085; A61 K 31/305 ; A61 K 31/415; A61 K 31/44; A61 K 31/455; A61 K 31/51; A61 K 31/525; A61 K 31/79; A61 K 33/18; A61 K 45/00; A61 K 31/79; A61 K 31:415

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWC
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☐ 2. Document ID: ES 2124328 T3, EP 613685 A1, DE 4306475 A1, EP 613685 B1, DE 59407247 G

L5: Entry 2 of 3

File: DWPI

Feb 1, 1999

DERWENT-ACC-NO: 1994-272802

DERWENT-WEEK: 199911

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TITLE: Liposomes contg. encapsulated chlorhexidine di:acetate or di:gluconate - for use in dentistry and oral hygiene, without causing discoloration of the teeth, and for general wound disinfection.

INVENTOR: ECHEVERRIA GARCIA, J J; GONZALEZ ENSENAT, P ; MAIERHOFER, G ; OLIVE MÓNCHO, J

PRIORITY-DATA: 1993DE-4306475 (March 2, 1993)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
ES 2124328 T3	February 1, 1999		000	A61K009/127
EP 613685 A1	September 7, 1994	G	005	A61K009/127
DE 4306475 A1	September 8, 1994		000	A61K009/127
EP 613685 B1	November 11, 1998	G	000	A61K009/127
DE 59407247 G	December 17, 1998		000	A61K009/127

INT-CL (IPC): A61K 7/00; A61K 7/16; A61K 7/22; A61K 9/127; A61K 31/155

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC
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☐ 3. Document ID: BE 803135 A, CH 576420 A, CH 613685 A, DD 108738 A, DE 2237904 A, DE 2237904 B, DE 2253276 A, DE 2253276 C, FR 2213267 A, GB 1429963 A, GB 1442670 A, JP 49055655 A, JP 49076853 A, SU 544365 A, US 3904659 A, US 3923845 A

L5: Entry 3 of 3

File: DWPI

Feb 4, 1974

DERWENT-ACC-NO: 1974-11345V

DERWENT-WEEK: 197407

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TITLE: Pure 1-nitro anthraquinone from mixts with dinitro anthraquinones - by selectively solubilising them in organic solvents with catalyst and base

PRIORITY-DATA: 1972DE-2253276 (October 31, 1972), 1972DE-2237904 (August 2, 1972)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
BE 803135 A	February 4, 1974		000	
CH 576420 A	June 15, 1976		000	
CH 613685 A	October 15, 1979		000	
DD 108738 A	October 5, 1974		000	
DE 2237904 A	March 28, 1974		000	
DE 2237904 B	June 4, 1980		000	
DE 2253276 A	May 9, 1974		000	
DE 2253276 C	November 26, 1981		000	
FR 2213267 A	September 6, 1974		000	
GB 1429963 A	March 31, 1976		000	
GB 1442670 A	July 14, 1976		000	
JP 49055655 A	May 30, 1974		000	
JP 49076853 A	July 24, 1974		000	
SU 544365 A	May 20, 1977		000	
US 3904659 A	September 9, 1975		000	
US 3923845 A	December 2, 1975		000	

INT-CL (IPC): C07B 11/00; C07C 76/06; C07C 79/36

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC
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L5: Entry 2 of 3

File: DWPI

Feb 1, 1999

DERWENT-ACC-NO: 1994-272802
DERWENT-WEEK: 199911
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TITLE: Liposomes contg. encapsulated chlorhexidine di:acetate or di:gluconate - for use in dentistry and oral hygiene, without causing discoloration of the teeth, and for general wound disinfection.

INVENTOR: ECHEVERRIA GARCIA, J J; GONZALEZ ENSENAT, P ; MAIERHOFER, G ; OLIVE MONCHO, J

PATENT-ASSIGNEE: ECHEVERRIA GARCIA J J (GARCI), GONZALEZ ENSENAT PJ J (ENSEI),
MAIERHOFER GENAT PJ J (MAIEI), OLIVE MONCHO JAT PJ J (MONCI)

PRIORITY-DATA: 1993DE-4306475 (March 2, 1993)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
ES 2124328 T3	February 1, 1999		000	A61K009/127
EP <u>613685</u> A1	September 7, 1994	G	005	A61K009/127
DE 4306475 A1	September 8, 1994		000	A61K009/127
EP <u>613685</u> B1	November 11, 1998	G	000	A61K009/127
DE 59407247 G	December 17, 1998		000	A61K009/127

DESIGNATED-STATES: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE AT BE CH DE DK ES
FR GB GR IE IT LI LU MC NL PT SE

CITED-DOCUMENTS: 01Jnl.Ref; EP 475160 ; EP 509338 ; JP63126820 ; WO 9220319

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
ES 2124328T3	February 16, 1994	1994EP-0102340	
ES 2124328T3		EP <u>613685</u>	Based on
EP 613685A1	February 16, 1994	1994EP-0102340	
DE 4306475A1	March 2, 1993	1993DE-4306475	
EP 613685B1	February 16, 1994	1994EP-0102340	
DE59407247G	February 16, 1994	1994DE-0507247	
DE59407247G	February 16, 1994	1994EP-0102340	
DE59407247G		EP <u>613685</u>	Based on

INT-CL (IPC): A61K 7/00; A61K 7/16; A61K 7/22; A61K 9/127; A61K 31/155

ABSTRACTED-PUB-NO: EP 613685A
BASIC-ABSTRACT:

Liposomes contain encapsulated chlorhexidine diacetate or chlorhexidine digluconate and consist of surfactants in addition to lipids which form double layers.

USE - The liposomes can be used in dentistry to prevent the formation of bacterial plaque and to treat wounds in the gums and periodically occurring aphthous inflammations of the oral mucous membranes, for peripheral bacterial contamination of root canals in endodontic therapy, to treat candida mycoses in the mouth and tongue

mucous membranes and the various forms of gingivitis and gingival hyperplasia. They are also used for the bacterial disinfection of epidermal, mesodermal and mucosal tissue. The liposomal chlorhexidine can be used in areas other than dentistry or oral hygiene e.g. for general wound disinfection, pre-operative skin disinfections, eye, bladder, pleural or peritoneal rinses and to impregnate gauze swabs.

ADVANTAGE - The liposomes are a stable and effective application form of chlorhexidine and are well tolerated by tissues. Side effects of chlorhexidine, e.g. discoloration of the teeth are greatly reduced or do not occur at all.

ABSTRACTED-PUB-NO: EP 613685B
EQUIVALENT-ABSTRACTS:

Liposomes contain encapsulated chlorhexidine diacetate or chlorhexidine digluconate and consist of surfactants in addition to lipids which form double layers.

USE - The liposomes can be used in dentistry to prevent the formation of bacterial plaque and to treat wounds in the gums and periodically occurring aphthous inflammations of the oral mucous membranes, for peripheral bacterial contamination of root canals in endodontic therapy, to treat candida mycoses in the mouth and tongue mucous membranes and the various forms of gingivitis and gingival hyperplasia. They are also used for the bacterial disinfection of epidermal, mesodermal and mucosal tissue. The liposomal chlorhexidine can be used in areas other than dentistry or oral hygiene e.g. for general wound disinfection, pre-operative skin disinfections, eye, bladder, pleural or peritoneal rinses and to impregnate gauze swabs.

ADVANTAGE - The liposomes are a stable and effective application form of chlorhexidine and are well tolerated by tissues. Side effects of chlorhexidine, e.g. discoloration of the teeth are greatly reduced or do not occur at all.

CHOSEN-DRAWING: Dwg.0/0

DERWENT-CLASS: B05 D21 E14
CPI-CODES: B07-A02; B10-A17; B12-M09; B12-M11F; B14-A01; B14-N03; B14-N05; B14-N06;
B14-N17; D08-B08; E10-A07; E10-A17A; E10-C04J2;

(19)



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(11) Veröffentlichungsnummer: **0 613 685 A1**

(12)

EUROPÄISCHE PATENTANMELDUNG

(21) Anmeldenummer: **94102340.0**

(51) Int. Cl.⁵: **A61K 9/127, A61K 31/155,
A61K 7/00, A61K 7/22**

(22) Anmeldetag: **16.02.94**

(30) Priorität: **02.03.93 DE 4306475**

(43) Veröffentlichungstag der Anmeldung:
07.09.94 Patentblatt 94/36

(84) Benannte Vertragsstaaten:
**AT BE CH DE DK ES FR GB GR IE IT LI LU MC
NL PT SE**

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Anmelder: **Olivé Moncho, Jorge
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Anmelder: **Echeverria Garcia, José Javier
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(74) Vertreter: **Patentanwälte Grünecker,
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(54) **Liposomen, enthaltend Chlorhexidindiacetat oder Chlorhexidingluconat.**

(57) Es werden Liposomen beschrieben, die Chlorhexidindiacetat oder Chlorhexidingluconat in Form von Liposomen enthalten und deren Zusammensetzung neben Doppelschicht bildenden Lipiden zusätzlich Tenside umfaßt.

Als Vorteile gegenüber der freien Form des Chlorhexidins können bei der liposomalen Darbietung die höhere und längere Wirksamkeit sowie geringere Nebenwirkungen angeführt werden.

EP 0 613 685 A1

Die Erfindung betrifft Liposomen, die zur speziellen Anwendung von Chlorhexidin für Desinfektion und medizinische Zwecke dienen.

Die Häufung bakterieller Plaques auf der Zahnoberfläche oder im Zahnfleischgewebe ist der hauptsächlich ätiologische Faktor für beginnenden Zahnverfall, Zahnfleischentzündung und Wurzelhautentzündung. In all diesen Fällen besteht die Vorsorge in erster Linie in der täglichen häuslichen Mundhygiene, d. h. Zähneputzen und Reinigung der Zahnzwischenräume, sowie in regelmäßigen zahnärztlichen Behandlungen, bei denen bakterielle Plaques und Zahnstein meist mit Hilfe von Schleifmaterialien entfernt werden. Obwohl diese Therapie- und Vorsorgemaßnahmen bei korrekter Durchführung durchaus wirkungsvoll sein können, sind sie doch in mancher Hinsicht beschränkt. So muß die häusliche Mundhygiene regelmäßig und sorgfältig erfolgen. Die Entfernung von Plaques aus den Zahnzwischenräumen erfordert manuelle Geschicklichkeit, die beispielsweise Kinder, ältere Menschen oder Behinderte nicht besitzen. Wie regelmäßig eine Zahnreinigung erfolgt, hängt außerdem stark von Motivation und Erziehung ab. Von noch größerer Bedeutung ist es jedoch, daß die vollständige Entfernung von bakteriellen Plaques und Zahnstein in fortgeschrittenen Fällen von Wurzelgabelung und Zahnfleischtaschen (mit einer Tiefe von mehr als 4 bis 5 mm vom Zahnfleischrand bis zum Grund des Defekts) extreme Schwierigkeiten bereitet. Dies ist selbst dann der Fall, wenn man einen Eingriff durchführt, um einen Zugang für die Reinigung zu erhalten. In vielen Fällen versagt die Behandlung von Periodontitis daher, weil es nicht gelingt, Zahnstein und verunreinigten Wurzelzement aus dem betroffenen Bereich während der Behandlung vollständig zu entfernen, oder weil der Patient nicht in der Lage ist, die Anzahl der bakteriellen Plaques während der Pflegephase unterhalb einer kritischen Grenze zu halten.

Auch die bisher wirkungsvollste chemische Methode, um die Bildung bakterieller Plaques zu verhindern, nämlich die Verwendung von Chlorhexidin als 1,2 bis 2 %ige Lösung zur zweimaligen täglichen Mundspülung von jeweils 2 Minuten, weist Nachteile auf. Besonders bei Rauchern, Tee- oder Kaffeetrinkern führt diese Methode zu Zahnverfärbungen, die einer täglichen Anwendung entgegenstehen. Zu den weiteren Ursachen der Zahnverfärbung gehören außerdem die Nekrose der Zahnpulpa, endodontische Zahnbehandlungen und die Alterung der Zähne, wobei es in letzterem Fall auch eine Rolle spielt, ob Abbaupartikel von bakteriellen Plaques (gefärbt beispielsweise durch Rauch, Nahrungsmittel oder Getränke) in die äußere Schicht des Zahnschmelzes eingebaut werden. Die relativ weit verbreitete Zahnverfärbung verursacht durch Chlorhexidin ist dosisabhängig. Auch wenn bei der Anwen-

dung einer 0,21 %igen Chlorhexidinlösung, verglichen mit einer 2 %igen, keine so drastische Verfärbung der Zähne auftritt, so bleibt sie doch ein großes, bisher ungelöstes Problem.

Andere Nebenwirkungen von Chlorhexidin, angewandt in der Mundhöhle, sind Geschmacksbeeinträchtigung, exfoliative Irritation der Mundschleimhaut (eine Folge der Alkoholkomponente in der Chlorhexidinlösung, meist 10 % Alkohol) und eine erleichterte Zahnsteinbildung.

Diese Nebenwirkungen schränken den Einsatz von Chlorhexidin stark ein und haben die Suche nach Alternativen stimuliert. Bis heute ist es nicht gelungen, einen anderen Wirkstoff zu finden, der dasselbe Wirkungsspektrum auf die Plaqueinhibierung und die Beseitigung von Plaque hat. Desgleichen ist bisher vergeblich versucht worden, Chlorhexidin haltige Formulierungen so zu verändern, daß keine Nebenwirkungen auftreten.

Die Lösung des Problems wurde erfindungsgemäß dadurch erreicht, daß Chlorhexidin in Liposomen entsprechend der Zusammensetzung in Anspruch 1 verkapselt werden. Spezielle Ausführungen werden durch die Unteransprüche wiedergegeben.

Unter Liposomen werden hier kugelförmige Vesikel aus einer oder mehreren Lipiddoppelschichten mit einem wässrigen Innenraum verstanden. Überraschend wurde festgestellt, daß sich Chlorhexidin in Liposomen, die neben den Doppelschicht bildenden Lipiden zusätzliche Tenside enthalten, stabil verkapseln läßt. Derartig liposomal verkapseltes Chlorhexidin kann nicht nur mit höherer Effizienz sondern auch mit lang andauernder Wirkung eingesetzt werden.

Zur Herstellung der Liposomen sind Doppelschicht bildende Membrankomponenten erforderlich, also amphiphile Substanzen wie Lipide oder Lipoide, d. h. Substanzen mit polaren, hydrophilen Kopfgruppen und unpolaren lipophilen Resten, wie sie für die Liposomenbildung üblicherweise verwendet werden. Zweckmäßig werden vorzugsweise physiologisch verträgliche, natürliche Lipide, wie Steroide, Phospholipide, Sphingolipide und Glykolipide verwendet. Bevorzugte Verbindungen umfassen Cerebroside und Ceramide, natürliche Phosphocholine, Phosphatidsäuren oder Phosphatidylglycerole, sowie gegebenenfalls Lysophospholipide und Fettsäuren und deren Derivate.

Erfindungsgemäß wurde festgestellt, daß die Chlorhexidin-Liposomen besonders rasch in die Haut und Schleimhaut penetrieren und besonders gut auf Zellen in vivo wirken, wenn den Lipiden, welche die Liposomenmembran bilden, zusätzlich Tenside zugesetzt werden. Die Art der zuzusetzenden Tenside hängt von ihrer physiologischen Verträglichkeit ab. Vorzugsweise werden Substanzen biologischer Herkunft eingesetzt, z. B. Gallensäuren und ihre Derivate, Glukoside, Maltoside und

Thioglukoside sowie Lysophospholipide. Besonders bevorzugte Verbindungen sind Natriumcholat, Natriumdesoxycholat, Natriumglykocholat, Natriumtaurocholat, aber auch Polyoxyethylene, Brij 56 und Brij 76, sowie Tween 80. Lipid (L) und Tensid (D) werden zweckmäßig in einem Molverhältnis L/D von 0,5 bis 40 eingesetzt, vorzugsweise 2 bis 20, besonders bevorzugt 3,1 bis 5,5.

Erfindungsgemäß werden die Liposomen hergestellt, indem man die lipiden Membrankomponenten und Chlorhexidin entweder als solche oder gelöst in einer geringen Menge eines physiologisch verträglichen, mit Wasser mischbaren Lösungsmittels, z. B. Alkohol, mit einer wässrigen Lösung der Tenside kombiniert. Die wässrige Lösung kann außerdem beispielsweise Salze, wasserlösliche Wirkstoffe oder Puffersubstanzen enthalten. Gegebenenfalls können weitere für die Liposomenherstellung übliche Zusatz- und Hilfsstoffe wie Gelbildner, Membranstabilisatoren und Konservierungsstoffe, z. B. Antioxydantien, sowie Oligopeptide und Proteine eingesetzt werden, die dem System zu jedem beliebigen Zeitpunkt entweder zusammen mit Lipiden und Tensiden oder aber getrennt von ihnen zugeführt werden können.

Die Vesikelbildung erfolgt durch Störung des Systems, indem man der heterogenen Mischung aus Lipiden und Tensiden mechanische Energie zuführt. Dies kann z. B. durch Schütteln, Rühren oder durch andersartige Einwirkung von Scherkräften, z. B. durch Filtrieren, erfolgen. Bevorzugt wird eine Störung des Systems mit Hilfe einmaliger Filtration. Man arbeitet hierbei vorzugsweise bei einem geringen Überdruck von 1 bis 6 bar. Der Porendurchmesser der Filter liegt zweckmäßig zwischen 0,1 und 0,8 µm, vorzugsweise zwischen 0,15 und 0,3 µm. Soll die Liposomenpräparation steril erhalten werden, so beträgt die obere Grenze des Porendurchmessers 0,22 µm. Die Herstellungstemperatur wird der Nutz- und Trägerstoffwahl angepaßt und liegt zweckmäßig zwischen 0 und 95 °C. Vorzugsweise arbeitet man in einem Temperaturbereich von 18 bis 70 °C; besonders bevorzugt für die Lipide mit fluiden Ketten ist der Temperaturbereich zwischen 18 und 38 °C, für die Lipide mit geordneten Ketten zwischen 45 und 60 °C.

Der pH-Wert liegt zweckmäßig in einem Bereich von 1 bis 10. Vorzugsweise wird im pH-Bereich zwischen 4 und 8, besonders bevorzugt zwischen 5 und 6,5 gearbeitet.

Als Ergebnis einer derartigen Präparationsmethode erhält man überwiegend unilamellare Liposom n. Der Anteil des zu verkapselnden Chlorhexidins ist abhängig vom jeweiligen Anwendungsgebiet und der Löslichkeit des Chlorhexidins. Zweckmäßig liegt die Chlorhexidinkonzentration zwischen 0,01 und 3 %, die der Membranbildner zwischen 0,5 und 10 %.

Die Verkapselung von Chlorhexidin in Liposomen führt zu einer signifikanten Dosisreduktion bei gleicher Wirksamkeit, verglichen mit der freien Form. Nebenwirkungen, wie z. B. die Zahnverfärbung, werden stark reduziert oder treten erst gar nicht auf.

Neben der Beseitigung und zur Vorbeugung von bakterieller Plaquebildung können die erfindungsgemäßen Chlorhexidin-Liposomen auch bei der chemischen Wundbehandlung von Zahnfleischtaschen, bei der Behandlung periodisch auftretender aphtöser Mundschleimhautentzündung, zur periapikalen bakteriellen Dekontamination von Wurzelkanälen bei der endodontischen Therapie, bei Candida-Mykosen an Mund- und Zungenschleimhaut, bei den verschiedenen Formen der Gingivitis und der gingivalen Hyperplasie und bei der bakteriellen Desinfektion epidermaler, mesodermaler und mukosaler Gewebe verwendet werden. Die Anwendung von liposomalem Chlorhexidin ist jedoch nicht auf den Bereich der Zahnmedizin oder der Mundhygiene beschränkt, sondern erstreckt sich auch auf andere medizinische Gebiete, wie z. B. der Wunddesinfektion, präoperative Hautdesinfektion, Augen-, Blasen-, Pleural- und Peritoneal-Spülungen und das Imprägnieren von Gazetupfern.

Mit der erfindungsgemäßen Liposomenpräparation wird demnach ein Mittel zur Verfügung gestellt, das nicht nur eine stabile sondern auch eine wirkungsvollere Anwendungsform von Chlorhexidin darstellt. Weitere Vorteile sind, daß das Verfahren einfach anzuwenden ist und die Chlorhexidinliposomen ausgezeichnet gewebeverträglich sind.

Beispiel

1 g Chlorhexidindiacetat bzw. Chlorhexidindiguconat und 4 g Sojalecithin werden in 4 ml Ethanol gelöst. 0,04 g Kochsalz und 0,56 g Natriumcholat werden in 43 ml Wasser bidest. gelöst. Beide Lösungen werden innig vermischt und die heterogene Mischung bei 5 bar sterilfiltriert. Die resultierende Liposomendispersion wird auf den gewünschten pH-Wert eingestellt und auf die in der nachfolgend geschilderten vorläufigen klinischen Cross over-Studie eingesetzte Chlorhexidinkonzentration verdünnt.

In der Studie wurde liposomales Chlorhexidin mit einer Chlorhexidinkonzentration von 0,05 % (LC) gegen ein handelsübliches Chlorhexidinprodukt mit einer Chlorhexidinkonzentration von 0,12 % (CC) getestet. Ein dritte Gruppe in der Studie wurde mit NaF-Lösung als Placebo behandelt (F).

An dieser Studie nahmen 7 Frauen teil, 21 bis 39 Jahre alt, jede mit mindestens 22 Zähnen, medizinisch gesund und ohne Zahnverfall, Gingivitis oder Periodontitis. Die Studie wurde eingeteilt in 3 Abschnitte von jeweils 4 Tagen. Für jeden Zeitab-

schnitt wurde folgendes Protokoll durchgeführt:

Nach sorgfältiger, professioneller Plaque-Entfernung, also Beginn mit einem Plaqueindex von Null (gemäß Silness Loe Klassifizierung), wurden die Teilnehmer gebeten, mit dem Zähneputzen aufzuhören und statt dessen Mundspülungen, 2 mal täglich 2 Minuten mit 10 ml einer der drei Lösungen durchzuführen und das über einen Zeitraum von 4 Tagen. Am Ende dieses Zeitabschnitts wurde ein Plaquedetektor (Trace, Lorvic) benutzt und ein bakterieller Plaqueindex für die 12 Vorderzähne bei jedem Teilnehmer bestimmt. Danach wurde den Teilnehmern gestattet, ihr gewohntes Zähneputzen für die folgenden 2 1/2 Tage wieder aufzunehmen, bevor eine neue 4 Tage-Testperiode mit einer der anderen Lösungen begonnen wurde.

Die erhaltenen Daten bezüglich der Plaqueindizes wurden an der Abteilung für Statistik der Universität Barcelona ausgewertet, wobei der Kruskal-Wallis Test für die Varianz herangezogen wurde. Die Ergebnisse zeigen einen signifikanten Unterschied zwischen CC und F, ebenso zwischen LC und F (in beiden Fällen Signifikanzlevel = 0,00001). Der Vergleich zwischen CC und LC zeigte keine Unterschiede (Signifikanzlevel = 0,0995). Statistisch signifikante Unterschiede wurden zwischen den Chlorhexidinlösungen und dem Placebo gefunden, wenn alle 3 Testlösungen zusammen ausgewertet wurden (Signifikanzlevel = 0,00001).

Während der Dauer der Studie wurden mit den Chlorhexidin-Liposomen keine Nebenwirkungen beobachtet, wie sie im Allgemeinen mit handelsüblichem Chlorhexidin bemerkt werden.

Basierend auf dem gegenwärtigen Wissensstand über Liposomen als Arzneistoffträger erscheint es vernünftig, sowohl eine substantielle Verbesserung als auch eine stark verbesserte Penetrationsfähigkeit von liposomalem Chlorhexidin zu erwarten, verglichen mit der freien Form des Chlorhexidins.

Patentansprüche

1. Liposomen, dadurch gekennzeichnet, daß sie Chlorhexidindiacetat oder Chlorhexidindigluconat verkapselt enthalten und ihre Zusammensetzung neben Doppelschicht bildenden Lipiden zusätzlich Tenside umfaßt.
2. Liposomen nach Anspruch 1, dadurch gekennzeichnet, daß die Lipide und/oder Tenside physiologisch verträgliche Verbindungen, bevorzugt natürlichen Ursprungs, sind.
3. Liposomen nach einem der Ansprüche 1 bis 2, dadurch gekennzeichnet, daß die Lipide ausgewählt sind aus der Gruppe der Phospholipide, Sphingolipide und Glykolipide.

4. Liposomen nach mindestens einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß die Tenside ausgewählt sind aus der Gruppe der Gallensäuren und ihrer Derivate, sowie deren physiologisch verträglichen Salzen.
5. Liposomen nach mindestens einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß die Tenside ausgewählt sind aus Natriumcholat, Natriumdeoxycholat, Natriumglykocholat, Natriumtaurocholat oder Natriumtaurodeoxycholat.
6. Liposomen nach mindestens einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß das molare Verhältnis von Lipiden (L) zu Tensiden (D) 0,5 bis 40, vorzugsweise 2 bis 20, besonders bevorzugt 3,1 bis 5,5 beträgt.
7. Liposomen nach mindestens einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß sie zusätzlich mindestens einen der üblichen Hilfs- und Zusatzstoffe, vorzugsweise Gelbildner und Membranstabilisatoren, umfassen.
8. Liposomen nach mindestens einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß die Doppelschicht bildenden Lipide und Chlorhexidin entweder als solche oder gelöst in einer geringen Menge eines mit Wasser mischbaren und zweckmäßig physiologisch verträglichen Lösungsmittels mit einer wässrigen Lösung von Tensiden kombiniert werden und die Liposomenbildung in der erhaltenen heterogenen Mischung durch Zufuhr mechanischer Energie, insbesondere durch Schütteln, Rühren oder Filtrieren, eingeleitet wird.



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Nummer der Anmeldung
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EINSCHLÄGIGE DOKUMENTE			
Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (InCL5)
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	* Seite 9, Zeile 38 - Seite 10, Zeile 5 *		
	* Seite 17, Zeile 34 - Zeile 35 *		
	* Seite 38 - Seite 40; Beispiele 62-107 *		
	* Seite 44 - Seite 47; Beispiele 151-175 *		
	* Seite 49 - Seite 52; Beispiele 236-237 *		
	* Seite 53 - Seite 54; Beispiel 243 *		
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	* Zusammenfassung *		

Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt			
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DEN HAAG		8. Juni 1994	Benz, K
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